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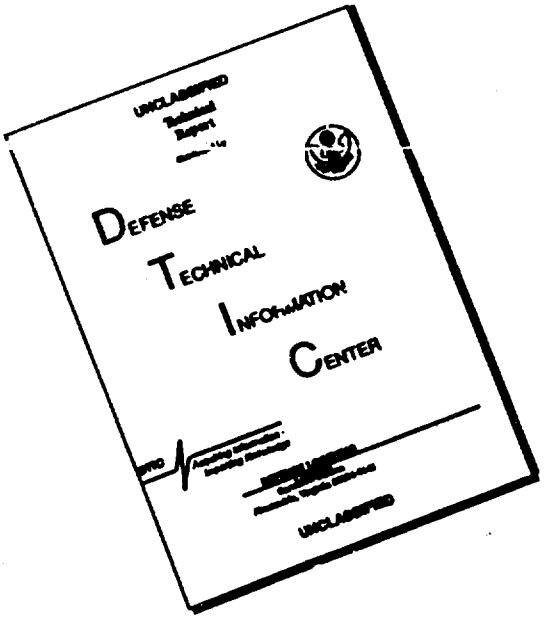

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15 August 1966

IMMUNOLOGY - INHIBITION OF HOMOLOGOUS AFFECTION IN MICE BY TREATMENT OF DONORS WITH VARIOUS ANTIGENS

IMMUNOLOGY - Inhibition of Homologous Affection in Mice by Treatment of Donors with Various Antigens.
A paper (*) by Messrs. PANAYOTIS LIACOPOULOS and E. BRUCE MERCHANT, presented by Mr. Bernard Halpern, before Group 13, Proceedings Committee of the Paris Academy of Science, on 5 July 1965.
C.R. Acad. Sc. 261: 1917-19, 1965

SUMMARY

Treatment of spleen-cell donor mice with an antigen gives rise to marked attenuation of the severity of the homologous affection in irradiated adult recipients. Of all the antigens used, the somatic antigen of Salmonella enteritidis, a polysaccharide, proved to be the most active.

In an earlier report, we noted that administration of heavy doses of an antigen inhibits production of antibodies in guinea pigs, and also inhibits development of delayed hypersensitivity to immunologically divergent antigens, when the latter are administered by injection several days after the beginning of treatment with the first antigen (1), (2) , (3). We also reported that the life-span of homologous skin grafts in animals treated with a non-divergent antigen, such as heterogenous gamma globulin, is considerably lengthened. (4) This inhibition of the transplant reaction was confirmed by a 50% reduction of mortality attributable to homologous affection induced in F_1 hybrids, which had been given spleen cells from parental donors previously treated with gamma globulins extracted from rabbits (5).

This paper reports the results of our study of the effect of treatment of donor animals with various antigens on the homologous affection induced in irradiated adult mice.

Technique

In all our experiments, the spleen cell donors were adult mice of the C 57/B1 strain. Recipients were adult mice of the C 3 H strain. The recipient animals were given a 500-r dose of radiation, 24 hours before the cell transplant. The donor animals had been treated for seven days before the transplant cells were taken with one of the following antigens: hemocyanine from Limulus polyphemus (Hcy), blood components of sheep, or the purified somatic antigen of Salmonella enteritidis (S.E. 211). On the seventh day of treatment, the cells of the spleens of the donor animals were dispersed, suspended in Hanks liquid, and counted in a hemocytometer. Varying quantities of spleen cells taken from treated animals as well as control animals were intravenously injected into the irradiated recipient animals.

The recipient animals which survived the homologous affection were subjected to skin grafts from the C 57/B1 mice, 35 days after the cell transfer.

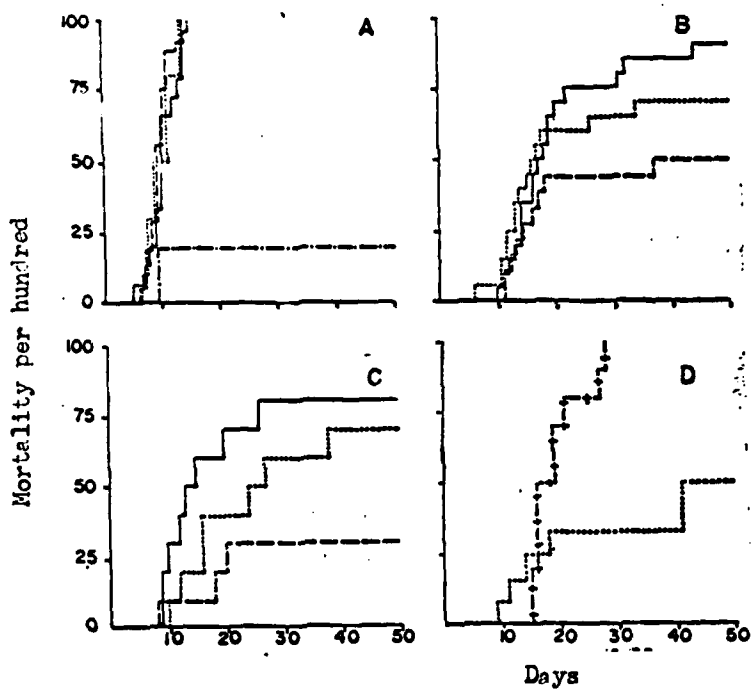
Results

In the combination of mouse-strains we chose (with C 57/B1 donors and C 3 H recipients), there is a high level of histo-incompatibility due to the difference in H_2 locus, and hence a very high mortality rate from the homologous affection. Thus all 55 recipients given injections of 100, 50, or 20 million spleen cells from untreated donors died within 15 days of the cell transplants (Figure A). When the dose was lowered to 10 million cells, four out of five of the animals survived.

Markedly different are the mortality curves for recipients of spleen cells from the donors subjected to prior treatment with different antigens. Figure B shows the pattern of mortality in animals receiving, respectively, 100, 50, or 20 million spleen cells taken from donors of the C 57/B1 strain pre-treated for seven days with 100 mg/diem of hemocyanine. Not only is animal mortality retarded, but a more substantial percentage of the recipient animals (higher or lower according to the dose of cells injected) finally survived.

Similar results were obtained in the experimental group where the C 57/B1 donors were pre-treated with sheep corpuseles /hematies de Mouton/ (10.10^9 units per mouse per day for seven days, by intraperitoneal injection). Of the recipient animals, 33% survived the homologous affection (Figure C).

In our final experiment, the donor animals were given 30 μg/day for 7 days of purified somatic antigen of Salmonella enteritidis (S.E. 211). In this experiments, one group of recipients got 200 million spleen cells from treated donors, while those of the second group got 50 million (Figure D). All the animals in the first group died, but they survived twice as long as the control animals, which had gotten ten times fewer cells (20.10^6).



Mortality rate in C 3 H mice exposed to 500-r radiation, and receiving spleen cells from C 57/Bl mice, either normal or pretreated with various antigens.

Donors C 57/Bl, recipients C 3 H, radiation dose 500-r.

+ - + - + -	200.10^6 spleen cells;
————	100 " " "
. . . . .	50 " " "
- - - - - -	20 " " "
- . - . - .	10 " " "

A - control ; B - treated with HCY, 100 mg/day ;
C - treated with sheep G. R. 10.10^9 /day ;
D - treated with S.E. 211, 30 μg/day.

among the group of mice given 50.10^6 cells, 50% of the animals clinically survived.

In order to discover whether or not a state of tolerance towards the tissues of the donor animals had been induced in the recipients surviving the homologous infection, we performed skin grafts from the C 57/Bl mice to both the survivors of the experiment and those of the control group which had received injections of 10.10^6 cells. The four animals from the control group rejected the grafts with a strong secondary reaction within four to five days. The 35 survivors, all of which had received cells from the spleens of treated donors, also rejected the graft, but far more slowly. It took them 10 to 20 days to slough off the alien skin-graft entirely.

Discussion

The results reported in this paper show that it is possible to change both the pattern and the outcome of a homologous affection, by treating the donor animals with an antigen which is immunologically different from the transplant antigens. This finding opens up some very interesting avenues. On the one hand, it would seem to afford a chance to save animals exposed to lethal doses of radiation. On the other, it apparently makes it possible to induce a specific immune-reaction tolerance for the tissues of another animal in the adult animal.

What we have proved here is that it is possible to induce a degree of tolerance in adult animals by injecting a large quantity of lymphoid cells (6). We have also shown that it is possible to induce tolerance by injecting a smaller number of cells (7) into animals exposed to radiation. This is possible, however, only in the combination of first-generation hybrid offspring as donor with the parent animal as recipient, a situation in which homologous affections do not develop anyway. In all other cases, the course of the disease led to the death of the recipient animal.

In the course of our earlier experiments we showed that, in a combination where there is mild histo-incompatibility, antigen treatment of the donor completely inhibits the homologous affection, and permits normal establishment of an immune-tolerance in the recipient (8). These latest results show that application of the same principle to a situation of very strong histo-incompatibility will produce an attenuation of the severity of the homologous affection, and will even save the lives of a significant percentage of the recipients (35 out of a total of 112).

Of course, it was not possible to induce immune-tolerance in the survivors. Nevertheless, such an achievement should theoretically be possible if we can find a way to make the recipient tolerate a heavier dose of donor cells. It is a fact that the somatic antigen of Salmonella anteritidis

did inhibit the homologous infection to at least as high a degree as did homocysteine, and did it with a dose 3,300 times smaller (30 μg/day as against 100 μg/day). And this would seem to be a hopeful sign that other antigens, more powerful or better suited to the circumstances, could produce a total inhibition of the homologous disease, and make possible the transfusion of a larger quantity of cells.

(*) Session of 28 June 1965.
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